Prevalence of Functional Gastrointestinal Disorders in Children and Adolescents in the Mediterranean Region of Europe

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BACKGROUND & AIMS: **Little is known about the prevalence of functional gastrointestinal disorders (FGIDs) in children from the Mediterranean area of Europe. We aimed to assess the prevalence of FGIDs in children and adolescents in this region.**

METHODS: **We collected data on 13,750 children (4–18 years old) enrolled in the Mediterranean–European Area Project, a school-based health study performed in Croatia, Greece, Israel, Italy, Jordan, Lebanon, Macedonia, Serbia, and Spain. Data were collected from March to June and in September of 2016. We analyzed data from 6602 students 4 to 10 years old (group A; mean age, 7.7 ± 1.9 y), and 7148 subjects 11 to 18 years old (group B; mean age, 13.8 ± 2.1 y). Children with FGIDs were identified based on answers to questionnaires on pediatric gastrointestinal symptoms, selected based on Rome III criteria.**

RESULTS: **In group A, the prevalence of FGIDs was 20.7%. The most frequent disorders were functional constipation (11.7%), irritable bowel syndrome (IBS, 4%), aerophagia (3.5%), and abdominal migraine (3.1%). The prevalence of abdominal migraine was significantly higher in girls than in boys ($P = .007$). In group B, the overall prevalence of FGIDs was 26.6%. The most frequent disorders were functional constipation (13.1%), abdominal migraine (7.8%), aerophagia (6.3%), and IBS (5.6%). In group B, FGIDs had a higher prevalence among girls than boys ($P < .001$). In both groups, we found significant differences in the prevalence of specific disorders among specific countries.**

CONCLUSIONS: **In an analysis of data on children 4 to 18 years old from the Mediterranean–European Area Project, we found FGIDs to be more frequent in girls. Functional constipation, aerophagia, abdominal migraine, and IBS are the most common disorders. However, the prevalence of FGIDs varies significantly among countries.**

Keywords: MEAP; Epidemiology; Survey; Abdominal Pain.

Abbreviations used in this paper: **AM, abdominal migraine; F, female; FAP, functional abdominal pain; FC, functional constipation; FGID, functional gastrointestinal disorder; GI, gastrointestinal; IBS, irritable bowel syndrome; M, male; MEAP, Mediterranean–European area project; QPGS-RIII, questionnaires on pediatric gastrointestinal symptoms based on Rome III criteria.**

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The Mediterranean–European Area project (MEAP) on functional gastrointestinal disorders (FGIDs) is a multistage project funded by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition. Its aim is to promote international collaboration in the field of FGIDs to evaluate the diagnostic–therapeutic approach to children with suspected FGIDs, to estimate the prevalence of these disorders, and to improve the dissemination of standardized diagnostic criteria.

FGIDs are common disorders characterized by chronic or recurrent gastrointestinal (GI) symptoms, not related to structural or biochemical abnormalities. Because of the lack of specific biological markers, FGIDs currently are defined according to the criteria established by the Rome Foundation, which are updated regularly.[1–3] The advantage of using the Rome criteria in clinical practice is that they permit a positive approach, avoiding unnecessary tests to rule out an organic cause, with a consequent beneficial effect on both patient's health and health care costs.

The prevalence of FGIDs based on Rome III criteria ranges between 12% and 29%. A recent study from Lewis et al,[4] who recruited a US sample of 949 mothers of children and adolescents aged 4 to 18 years, found an overall prevalence of 23.1% based on parental report. Several studies attempted to evaluate the epidemiology of FGIDs according to Rome III criteria. However, most of them assessed the prevalence only in small community samples,[5,6] in single countries (eg, Greece or Norway),[7,8] in selected age ranges (eg, adolescents),[9] or focused mainly on abdominal pain–related disorders.[10–12] In the Mediterranean–European area the prevalence of FGIDs is poorly defined. Therefore, as part of the MEAP, we launched an international multicenter study to assess the prevalence of FGIDs in a large community sample of children and adolescents from the Mediterranean–European area. The first stage of the MEAP study consisted of a survey on the diagnostic and therapeutic approaches to children with suspected FGIDs by general pediatricians from European–Mediterranean countries, and showed inadequate knowledge and use of the Rome III diagnostic criteria and a lack of standardization in the therapeutic approach to FGIDs.[13] The second stage translated the standardized Questionnaires on Paediatric Gastrointestinal Symptoms based on Rome III Criteria (QPGS-RIII), for non–English-speaking countries, to assess the prevalence of FGIDs. The present study represented the third stage of the MEAP and was conducted through the existing international research network established during the first stage of the project, with the aim of assessing the prevalence of FGIDs in children and adolescents from the Mediterranean–European area.

Methods

This school-based, prospective, multicenter study was performed in 9 countries in the Mediterranean–European area: Croatia, Greece, Israel, Italy, Jordan, Lebanon, Macedonia, Serbia, and Spain. To obtain a nationwide sample, we surveyed subjects aged 4 to 18 years enrolled in schools (nursery schools, primary schools, and secondary schools) distributed throughout the national territory of the involved countries, including both large cities and small centers. For each city, the schools were selected randomly from a list of all the schools available in the territory. The criteria for the selection of the schools were the same in all involved countries. In most of the countries only public schools were included, with the exception of Jordan, Spain, and Lebanon, which also included private schools. The National coordinator for each country contacted the directors of the selected schools to obtain permission to conduct the study. From each school, randomly selected classes were surveyed. The parents/legal guardians and their children then were invited to a meeting for an explanation of the study procedures and the collection of consent to participate. Children were included if consent was provided and in the absence of alarm symptoms suggestive of an organic disease. Informed consent was obtained by parents/legal guardians of the involved children, and by subjects older than 10 years of age. To ensure complete understanding, the printed versions of the study questionnaires were completed in the presence of the study staff, who were available for clarifications.

The study was approved by the Ethic Committees of the coordinating center (University of Naples) and of all the participating centers, and was conducted in accordance with the Declaration of Helsinki and Guidelines for Good Clinical Practice. All data were collected anonymously.

Rome Questionnaires

The prevalence of FGIDs was assessed using the QPGS-RIII translated for non–English-speaking countries during the second stage of the MEAP. The QPGS-RIII is a validated questionnaire, specifically designed to diagnose FGIDs in children and adolescents.[14] For each participating country, the principal investigators translated the original English version of the questionnaires into the native language of their countries. Then, a different person from each country translated the questionnaires back to English; finally, the original questionnaires and the back-translated questionnaires (both in English) were compared to ensure that the meaning was not modified during the translation process. In Israel, the questionnaire also was fully validated by the Rome Foundation; in Greece, the pre-existing official translation of the Rome III questionnaires was used.[7]

The parent-report form was used for subjects between ages 4 and 10 years, and the self-report form was used for subjects between ages 11 and 18 years.

Data Collection and Statistical Analyses

Data were collected from March to June, and in September 2016, during school time. The national data from each country were entered into a Microsoft Excel database (Microsoft, Redmond, WA) specifically designed for the study. All data were sent to the coordinating center (University of Naples) for data analysis. For each FGID an algorithm was created to diagnose the disorder according to the QPGS-RIII scoring system. In case of lack of answers necessary to diagnose a specific disorder, the subject was considered missing for that disorder and was excluded from the prevalence analysis. Likewise, in the case of lack of data on sex, the subject was considered as missing and was excluded from the analysis. These data are available from the authors upon request.

Quantitative variables were synthetized using means ± SD whereas categoric variables were described using absolute frequencies and percentages. The prevalence of each disorder was estimated by calculating the ratio between the affected subjects and the total number of valid cases for each disorder. The corresponding 95% CIs were computed using the Clopper–Pearson exact method. Comparisons between ages, sex, and countries were assessed using the chi-square test or the Fisher exact test when appropriate. The issue of multiplicity in country comparison was addressed using the Bonferroni procedure; for each comparison, statistical significance was determined as $P < .001$. All the statistical analyses were performed using the statistical platform R. The R code for the assignment of diagnosis is available from the authors upon request.

Results

We surveyed a total of 13,750 subjects between 4 and 18 years of age from 9 countries in the Mediterranean–European area. The mean response rate was 69%. The number of subjects surveyed and the response rate in each participating country are shown in Table 1. Specifically, we included 6602 subjects between ages 4 and 10 years (group A: mean age, 7.7 ± 1.9 y; girls [females (F)], 50.8%), and 7148 subjects between ages 11 and 18 years (group B: mean age, 13.8 ± 2.1 y; F, 50.6%). The prevalence values of all FGIDs defined according to Rome III criteria in both study groups are summarized in Table 2.

In subjects ages 4 to 10 years, the overall prevalence of FGIDs was 20.7% (F, 46.5%). One FGID was identified in 17.4% of the subjects, a combination of 2 FGIDs was identified in 2.8%, 3 FGIDs were identified in 0.4%, and of 4 FGIDs were identified in 0.1%. The most frequent disorders were functional constipation (FC) (11.7%), irritable bowel syndrome (IBS) (4%), aerophagia (3.5%), and abdominal migraine (AM) (3.1%). In this age group we did not find differences in the overall prevalence of FGIDs between sexes. However, focusing on single disorders, we found that the prevalence of AM (boys [males (M)] of 2.5% vs F 3.8%; $P = .007$) was significantly higher in girls than in boys. In contrast, nonretentive fecal incontinence was more prevalent in boys (M, 0.8% vs F, 0.3%; $P = .036$). The prevalence of all FGIDs in children ages 4 to 10 years in the different countries is shown in Table 3.

In subjects ages 11 to 17 years, the overall prevalence of FGIDs was 26.6% (F, 55%), with a single FGID recorded in 19.5% of the subjects, 2 FGIDs in 6%, 3 FGIDs in 1%, and 4 FGIDs in 0.1%. The most frequent disorders were FC (13.1%), AM (7.8%), aerophagia (6.3%), and IBS (5.6%). In this age group we found that FGIDs were significantly more frequent in girls (M, 23.4% vs F, 29.1%; $P < .001$). Looking at the different countries separately, we found that the prevalence of FGIDs was significantly higher in girls in Croatia (M, 21.8% vs F, 37.1%; $P < .001$), Serbia (M, 4.4% vs F, 10.2%; $P = .005$), and Spain (M, 22.1% vs F, 28.5%; $P = .045$), and showed a trend toward significance in Italy (M, 17.8% vs F, 24.8%; $P = .007$).

A higher prevalence in girls compared with boys also was found with regard to single FGIDs, such as aerophagia (7.5% vs 5.1%, respectively; $P < .001$), functional

Table 1. Number of Subjects, Mean Age, Sex, and Response Rate in Each Participating Country

	Group A: 4–10 y				Group B: 11–18 y					
Country	N	M, %	F, %	Age, *y*, means ± SD	N	M, %	F, %	Age, *y*, means ± SD	Total	Response rate, %
Croatia	809	48.9	51.1	6.6 ± 2	907	30.7	69.3	14.8 ± 1.9	1716	80
Greece	727	58.3	41.7	9.9 ± 0.5	589	54.9	45.1	16.8 ± 0.7	1316	58
Israel	399	50.6	49.4	7.1 ± 1.9	823	42.4	57.6	13.8 ± 2.2	1222	52
Italy	1070	50.2	49.8	8.1 ± 1.8	1048	50.2	49.8	13.3 ± 1.9	2118	79
Jordan	822	50.7	49.3	8.1 ± 1.4	772	56	44	14 ± 1.8	1594	80
Lebanon	537	46.6	53.4	7.3 ± 1.9	470	50.6	49.4	14.1 ± 1.8	1007	83
Macedonia	711	48.8	51.2	8 ± 1.8	844	50.3	49.7	14.7 ± 2.2	1555	74
Serbia	828	37.4	62.6	7.2 ± 1.6	829	46.6	53.4	12.6 ± 1.4	1657	65
Spain	699	48.6	51.4	7.2 ± 1.9	866	49.2	50.8	14.1 ± 2.2	1565	52
Total	6602				7148				13,750	69

Table 2. FGID Prevalence in Children and Adolescents

Disorder	Group A: 4–10 y, n = 6602			Group B: 11–18 y, n = 7148		
	Valid cases	N (prevalence)	95% CI	Valid cases	N (prevalence)	95% CI
Vomiting and aerophagia						
Adolescent rumination syndrome	6269	2 (0.03%)	0.0–0.1	6865	8 (0.1%)	0.0–0.2
Cyclic vomiting syndrome	6184	19 (0.3%)	0.2–0.5	6797	37 (0.5%)	0.4–0.7
Aerophagia	5956	209 (3.5%)	3.0–4.0	6509	413 (6.3%)	5.8–7.0
Abdominal pain–related FGIDs						
Functional dyspepsia	6453	23 (0.3%)	0.2–0.5	7039	38 (0.5%)	0.4–0.7
Irritable bowel syndrome	6117	243 (4%)	3.5–4.5	6862	383 (5.6%)	5.0–6.1
Abdominal migraine	6061	189 (3.1%)	2.7–3.6	6858	535 (7.8%)	7.1–8.5
Functional abdominal pain	6101	31 (0.5%)	0.3–0.7	6908	26 (0.4%)	0.2–0.6
Functional abdominal pain syndrome	6156	15 (0.2%)	0.1–0.4	6944	40 (0.6%)	0.4–0.8
Constipation and incontinence						
Functional constipation	5899	688 (11.7%)	10.8–12.5	6325	832 (13.1%)	12.3–14.0
Nonretentive fecal incontinence	6269	34 (0.5%)	0.4–0.7	6680	26 (0.4%)	0.2–0.6

FGIDs, functional gastrointestinal disorders.

dyspepsia (0.8% vs 0.3%, respectively; $P = .008$), IBS (6.4% vs 4.5%, respectively; $P = .001$), and AM (9.7% vs 5.5%, respectively; $P < .001$). Interestingly, in this age group we also found statistically significant differences in the prevalence of specific FGIDs among some of the involved countries. The prevalence of FGIDs in subjects ages 11 to 18 years in the different countries is shown in Table 4.

Finally, we detected statistically significant differences ($P < .001$) in the prevalence of specific disorders among some of the participating countries. These comparisons are summarized in Table 5.

Discussion

This school-based cross-sectional study recruited a large number of children and adolescents nationwide for each of the 9 included countries from the Mediterranean–European area, with the aim of evaluating the prevalence of FGIDs according to Rome III criteria by using an already established international network.

Our main finding was that 20.7% of children aged 4 to 10 years and 26.6% of adolescents aged 11 to 18 years fulfilled the Rome III criteria for at least 1 FGID. Although the data for the Mediterranean area are scarce, our findings are comparable with other studies evaluating the prevalence of all FGIDs according to Rome III criteria. Our results were similar to those of the study from Bouzios et al[7] that included 1658 Greek children between ages 4 and 18 years that found a prevalence of 23.5%, the study from Saps et al[5] including 373 Colombian children that reported a prevalence of 29%, or the earlier-mentioned study from Lewis et al[4] in which the prevalence of FGIDs was 23.1%. In the present study, unlike most of the previous studies conducted in single countries, we separated the analysis of children

Table 3. FGID Prevalence (%) in Children Between Ages 4 and 10 Years, in All Involved Countries

	Croatia	Greece	Israel	Italy	Jordan	Lebanon	Macedonia	Serbia	Spain
Vomiting and aerophagia									
Adolescent rumination syndrome	0	0	0.2	0	0	0.2	0	0	0
Cyclic vomiting syndrome	0.5	0.3	0.3	0.1	0.6	0.7	0	0	0.4
Aerophagia	10.4	1.1	1.6	1.9	5.3	4	1.9	0.7	3.6
Abdominal pain–related FGIDs									
Functional dyspepsia	0.1	0.1	0.5	0.6	0.1	0.7	0.1	0.5	0.4
Irritable bowel syndrome	4.3	2.2	6.7	4.6	3.4	4.1	2.2	1.3	7.3
Abdominal migraine	1.9	2.7	5.4	2.0	3.0	3.8	3.0	0.7	6.9
Functional abdominal pain	0	0.3	0.8	0.5	0.1	0.6	0.3	0	2.1
Functional abdominal pain syndrome	0.2	0.1	0.8	0.2	0.1	0.4	0	0	0.6
Constipation and incontinence									
Functional constipation	4.6	13.4	9.8	18.6	14.4	11.4	7.6	4.4	17.9
Nonretentive fecal incontinence	0.7	0.4	0.8	0.1	0.8	0.4	0.1	0	1.7

FGIDs, functional gastrointestinal disorders.

Table 4. FGIDs Prevalence (%) in Children Between Ages 11 and 18 Years, in All Involved Countries

	Croatia	Greece	Israel	Italy	Jordan	Lebanon	Macedonia	Serbia	Spain
Vomiting and aerophagia									
Adolescent rumination syndrome	0.1	0.3	0.2	0	0.1	0	0.1	0	0.1
Cyclic vomiting syndrome	0.4	0	0.9	0	2.3	0.4	0.4	0.1	0.6
Aerophagia	18.3	6.3	6.0	2.6	7.3	4.4	6.0	2.9	3.0
Abdominal pain–related FGIDs									
Functional dyspepsia	0.1	0.2	1.1	0.6	0.6	1.1	0.1	0.2	0.9
Irritable bowel syndrome	8.4	5.8	10.6	3.8	4.4	6.2	3.5	2.0	6.2
Abdominal migraine	10.7	5.2	16.2	5.1	5.8	4.7	6.6	1.9	11.9
Functional abdominal pain	0	0.7	0.4	0.8	0.3	0.6	0.1	0	0.6
Functional abdominal pain syndrome	0.6	0.5	0.7	1.1	0.3	0.2	0.4	0.7	0.2
Constipation and incontinence									
Functional constipation	6.9	15.8	16.6	14	20	14.6	22.3	2.5	8.8
Nonretentive fecal incontinence	0	0	0.6	0.1	0.1	0.2	0.9	0.8	0.6

FGID, functional gastrointestinal disorders.

aged 4 to 10 years from that of adolescents aged 11 to 18 years to identify age-dependent differences in the prevalence of FGIDs and in particular information on FGIDs prevalence in younger children in whom data are scarce worldwide.

Our data show that the prevalence of most FGIDs is higher in adolescents compared with children, and in girls compared with boys, even if the difference in the prevalence related to sex becomes statistically significant only in older children. Increased prevalence in girls is well known, and has been described in previous studies in single countries.[5,7,9,15] The same is true for age-related differences between sexes, which have been described previously by others, such as in the study from Sagawa et al,[9] which included 3976 Japanese adolescents ages 10 to 17 years.

Regarding the age-related differences in the prevalence, it has to be stated that because of the lack of correlation between children's and parents' answers on the QPGS-RIII, a comparison between the 2 groups is not possible because the differences could be owing either to age or to the reporter.

Evaluating the various FGIDs we found that, in accordance to single-country studies,[4,7,5,15] the most frequent FGID in both age groups was FC, with a prevalence ranging between 11.7% and 13.1%. Furthermore, the prevalence of IBS in our study was similar to previous reports from single countries,[5,9,12,15–17] and the same was true for aerophagia.[4,7,15] In contrast to previous studies,[5,9,11,15–17] we found a higher prevalence of AM, representing one of the most frequent disorders in our population, and a lower prevalence of functional abdominal pain (FAP) and FAP syndrome, in accordance with the studies by Lewis et al[4] and Bouzios et al.[7] It can be argued that AM rarely is diagnosed in clinical practice, whereas FAP and FAP syndrome are encountered much more commonly. The reason for these differences is unknown, and can be justified only partially by the diagnostic criteria used. In fact, it is known that the prevalence of AM estimated with Rome III criteria tends to be 4-fold higher than with Rome II criteria, probably because of the Rome III criteria's low negative predictive value, which can lead to the incorrect diagnosis of other FAP disorders such as AM, as stated by the Rome IV Committee.[3] However, all the other studies considered used the Rome III criteria, but not all of them found such a high prevalence of AM. Possible variations among the countries in the microbiome, diet, and genetic background could be a plausible hypothesis for the differences obtained in different studies.

Finally, we found significant variations in the prevalence of some FGIDs among different European countries. For example, we reported a significantly lower prevalence of FC in Croatia and Serbia, a higher prevalence of aerophagia in Croatia, a higher prevalence of AM in Israel and Spain (especially in younger children), and a higher prevalence of IBS in Israel. The reasons for these differences are not clear. However, considering the multifactorial pathogenesis of FGIDs, it can be speculated that they represent the result of the earlier-mentioned variability in the environment, diet, microbiome, and genetic background among the involved countries and suggest that the results of single-country studies may not be generalized. In addition, because the translations of the QPGS-RIII have not been validated in most of the countries, it also is possible that variations in understanding of the terminology among children of different countries could explain some of the differences found. Moreover, we found that Serbian prevalence values tended to be lower than in other countries for the majority of the disorders. This could be owing to the higher number of missing data from Serbian questionnaires compared with other countries.

There were some limitations to our study. This was a parent and patient report, which suffered from the potential biases inherent to this type of reporting. Also, our study did not collect data on demographic characteristics, socioeconomic status, or diet. The lack of

Table 5. Country Comparison of FGID Prevalence in All Involved Countries

	Croatia (A)	Greece (B)	Israel (C)	Italy (D)	Jordan (E)	Lebanon (F)	Macedonia (G)	Serbia (H)	Spain (I)
4–10 years									
Aerophagia	B, C, D, E, F, G, H, I				B, C, D, H	B, H			H
Irritable bowel syndrome			B, G, H	H					B, E, G, H
Abdominal migraine			A, D, H			H			A, B, D, E, G, H
Functional abdominal pain									A, B, D, E, G
Functional constipation		A, G, H	A, H	A, C, F, G, H	A, G, H	A, H			A, C, G, H
Nonretentive fecal incontinence									D, G, H
11–18 years									
Cyclic vomiting syndrome					A, B, D, F, G, H				
Aerophagia	B, C, D, E, F, G, H, I	D	D		D, H, I		D		
Irritable bowel syndrome	D, G, H	H	D, E, G, H			H			H
Abdominal migraine	B, D, E, F, H	H	A, B, D, E, F, G, H	H	H		H		B, D, E, F, G, H
Functional constipation	H	A, H, I	A, H, I	A, H, I	A, H, I	A, H	A, D, F, H, I		H

NOTE. Each country is identified by a letter (eg, Croatia = A; Greece = B; and so forth). Each column refers to a single country; the letters in the rows identify the countries in which the prevalence is significantly lower compared with the country of the column. The prevalence of each disorder in all the countries is shown in Tables 3 and 4.

demographic data do not ensure that the sample is representative of the country prevalence. Moreover, knowledge of these data could have allowed a better understanding of the reported intercountry differences. However, our study was not originally launched to evaluate the impact of these factors on the prevalence of FGIDs. In addition, most of the QPGS-RIII translations have not been validated. Nevertheless, the forward/backward translation, and the availability of the study staff to ensure understanding of the QPGS-RIII, should have ensured the reliability of the questionnaires. Finally, because methodologies in the different study sites have not been checked, it is possible that subtle differences in the sampling procedures or translation issues have contributed to the country differences.

The major strength of this study was the large number of participants. Also among the strengths was the central analysis of the data, securing the uniformity in both symptom-based diagnosis of FGIDs and in the processing of the missing data.

This study evaluated the prevalence of FGIDs in a very large sample of children and adolescents from the Mediterranean–European area. Our findings confirm that FGIDs are found commonly in children and adolescents, especially girls, and that their frequency increases with age. Most interestingly, the prevalence of FGIDs varied significantly among different Mediterranean countries, suggesting that in fact there may be differences in genetic background, diet, environment both physical and socioeconomic, and microbiome. Further multinational studies are needed to evaluate the impact of demographic characteristics, socioeconomic status, and diet on the occurrence of FGIDs, allowing a better understanding of the reported intercountry differences in the prevalence of the various FGIDs.

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Conflicts of interest
The authors disclose no conflicts.

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